

# Marijuana:

## *The Highs and Lows*

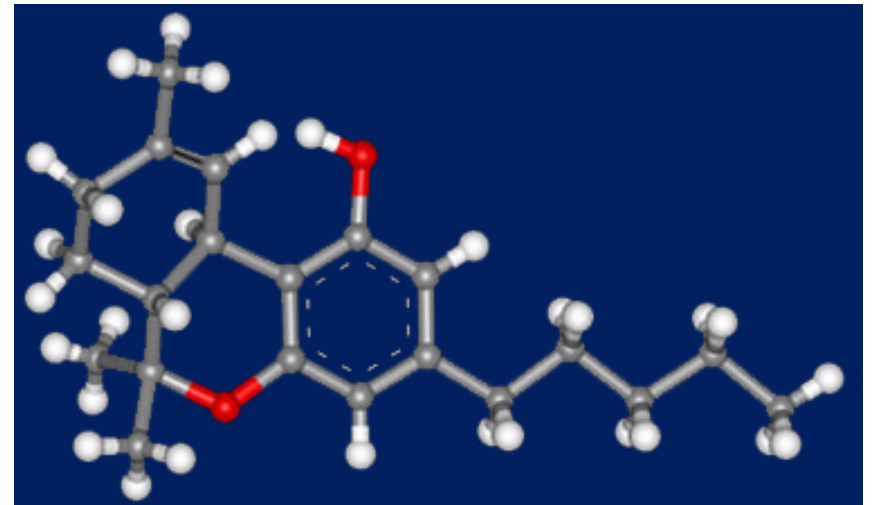


Nora D. Volkow, MD  
Director  
National Institute  
on Drug Abuse

# Marijuana is the Most Commonly Used Illicit Drug In the U.S.



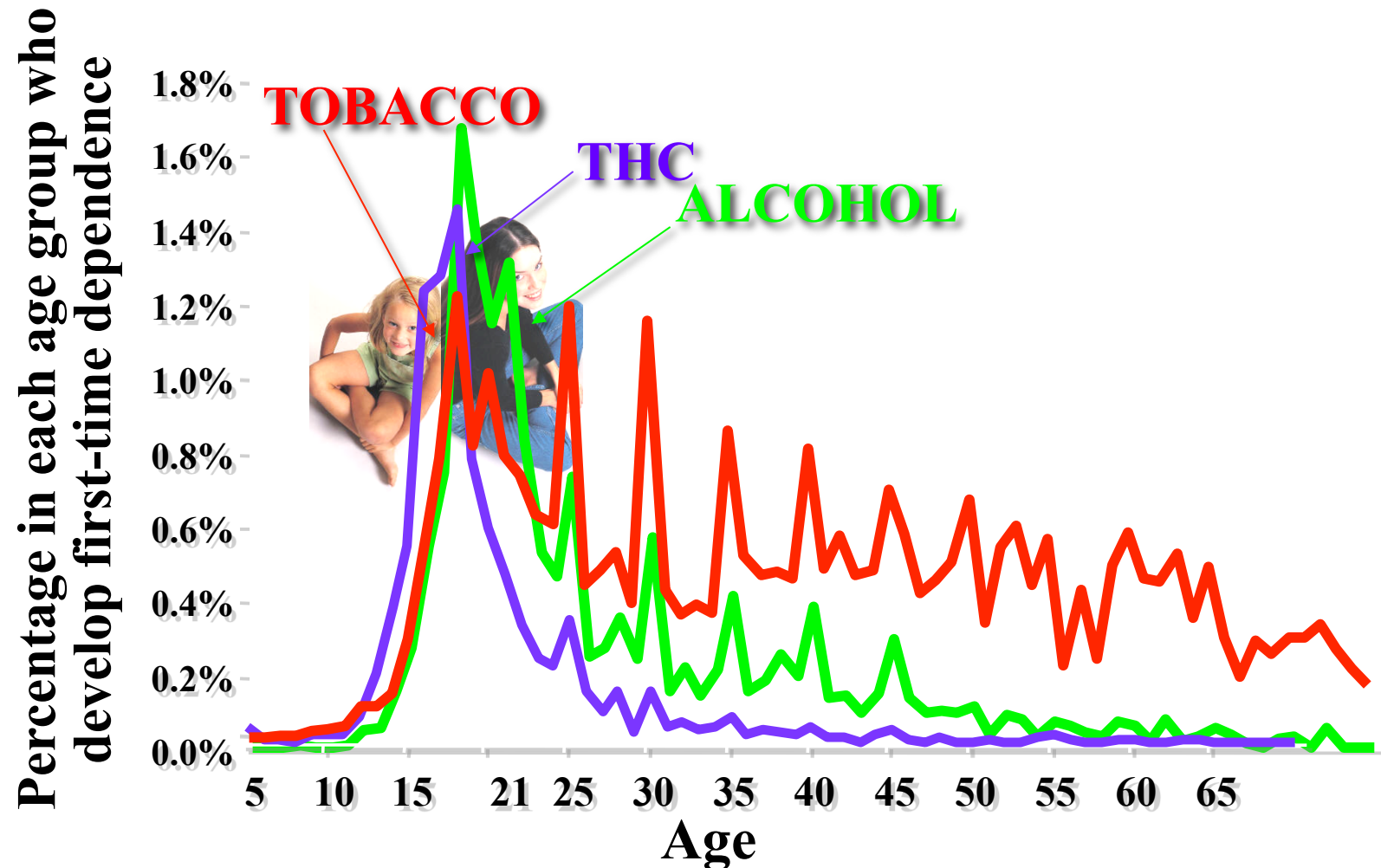
- Over **114 million** Americans have tried it at least once
- An estimated **2.4 million** Americans used it for the first time in 2013



**Tetrahydrocannabinol (THC)**  
**Active Ingredient in Marijuana**

# ADDICTION IS A DEVELOPMENTAL DISEASE

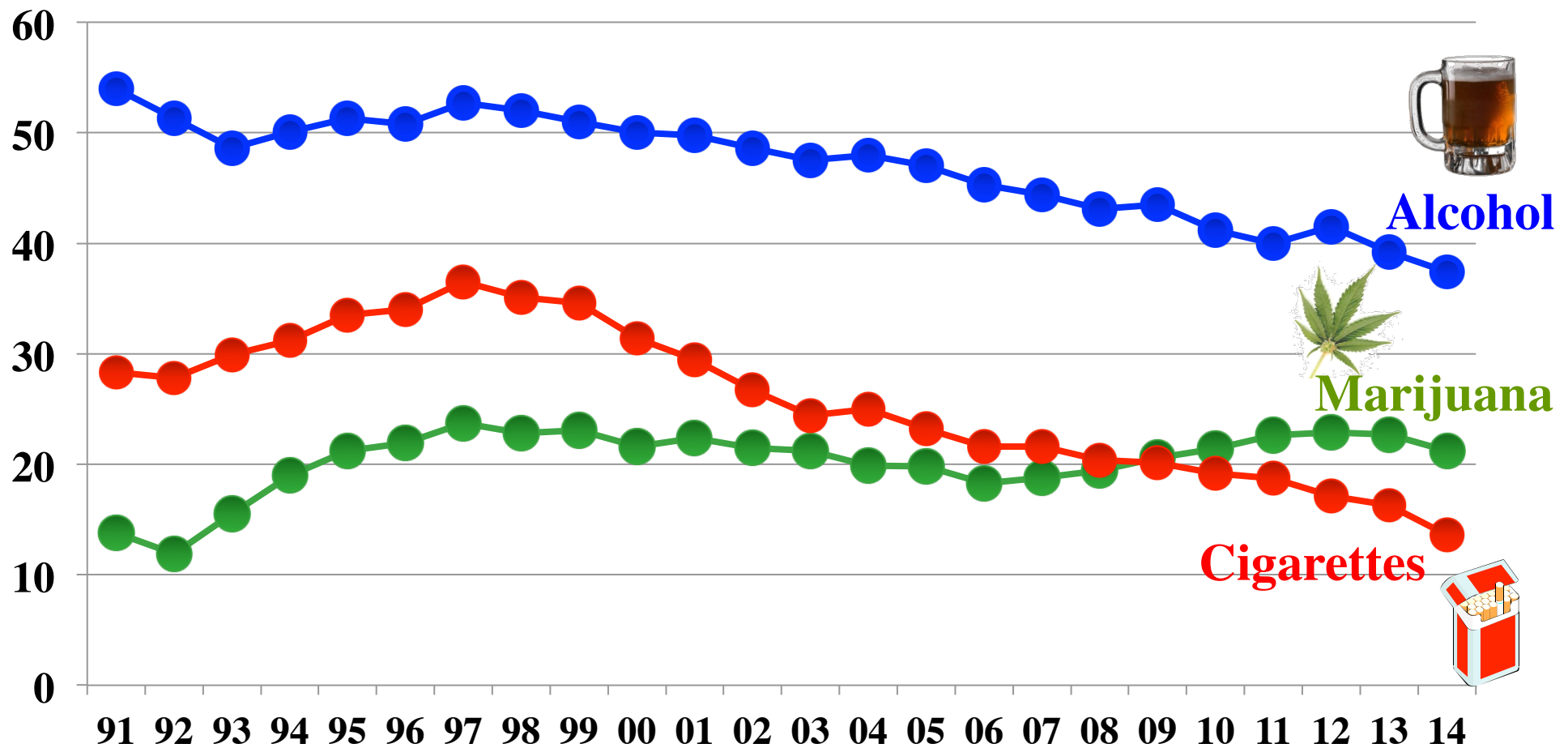
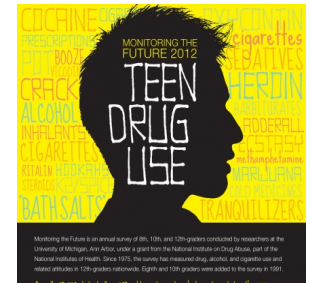
*it starts in adolescence and childhood*



Age at **tobacco**, at **alcohol** and at **cannabis** use dependence as per DSM IV

*NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003.*

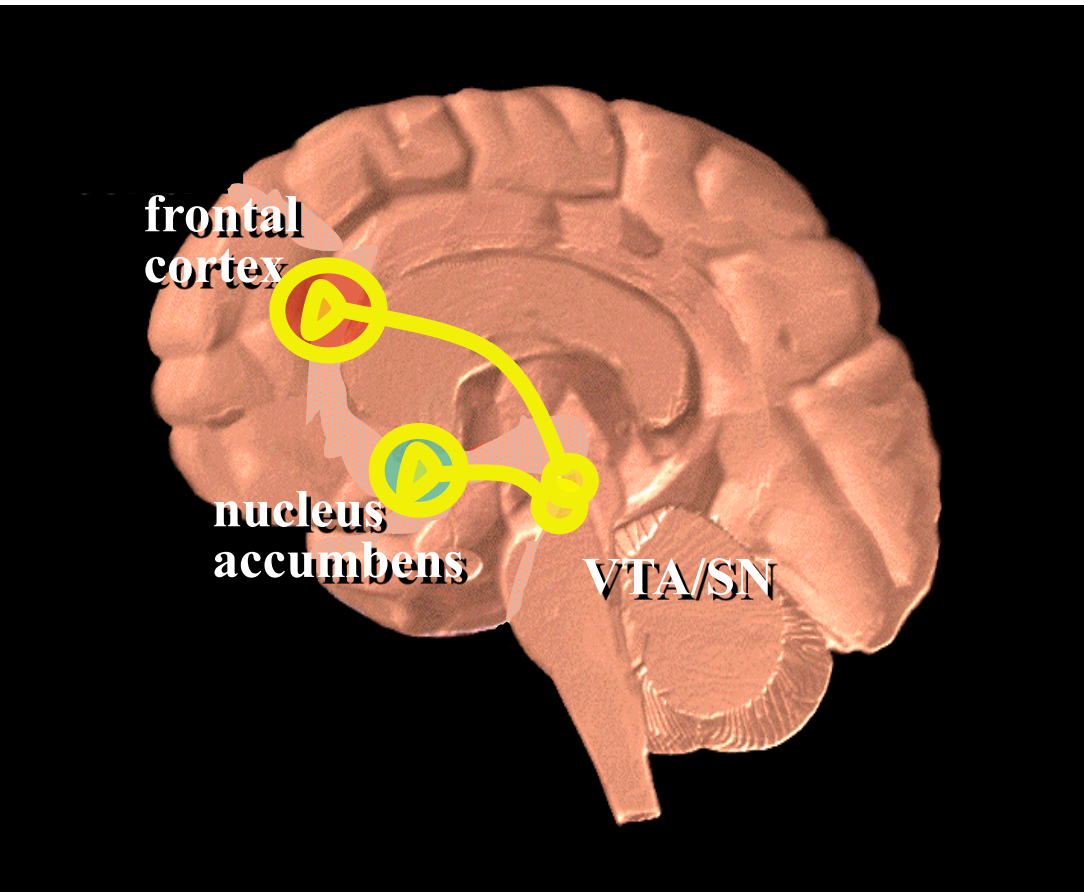
# Percentage of U.S. 12<sup>th</sup> Grade Students Reporting Past Month Use of Cigarettes, Marijuana and Alcohol



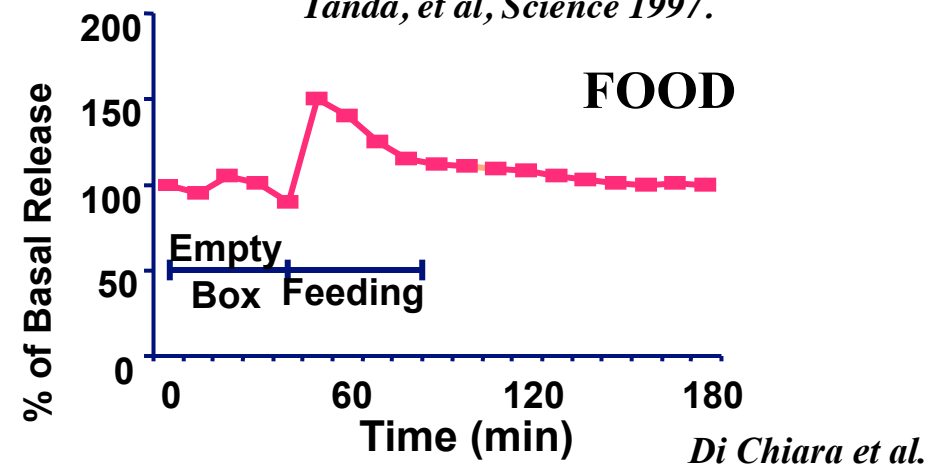
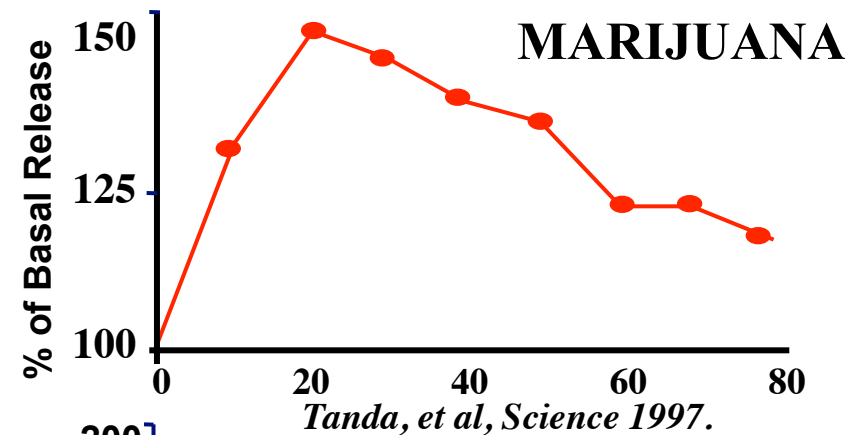
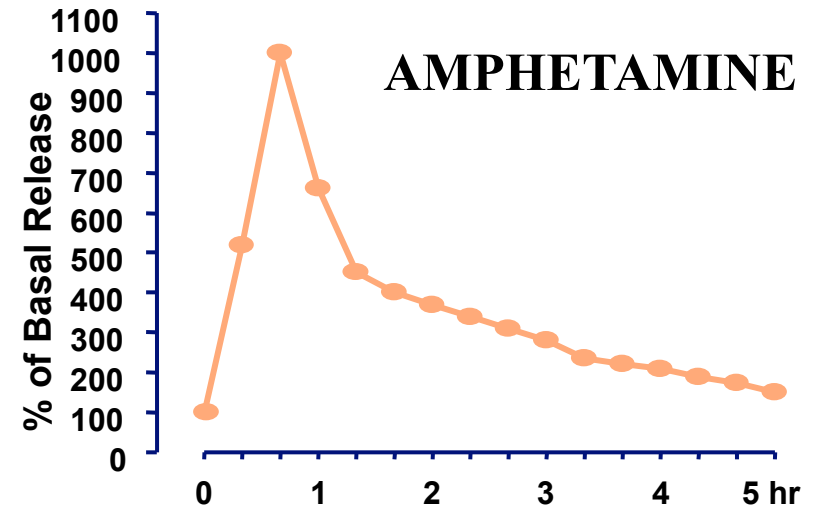
*SOURCE: University of Michigan, 2014 Monitoring the Future Study.*



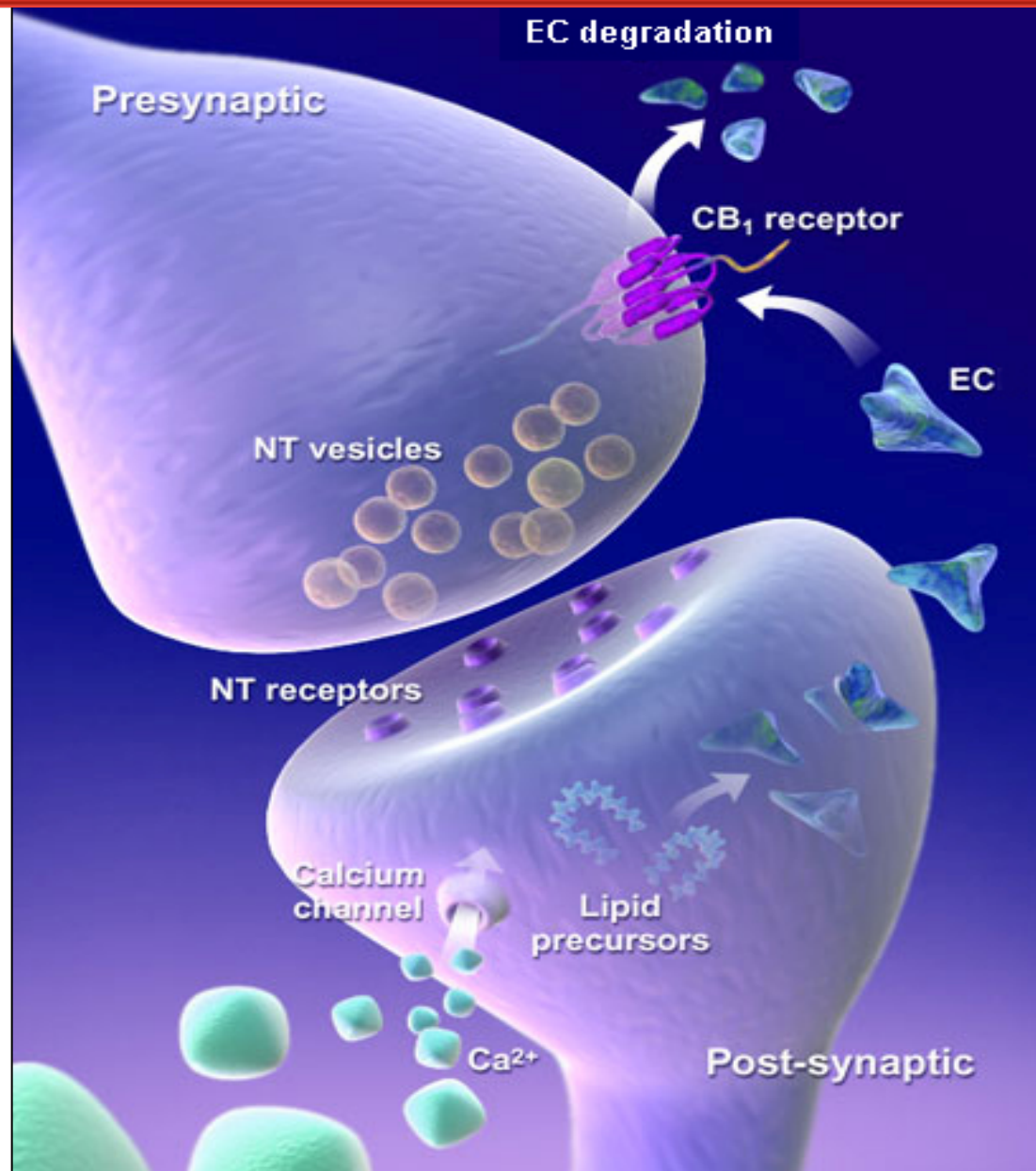
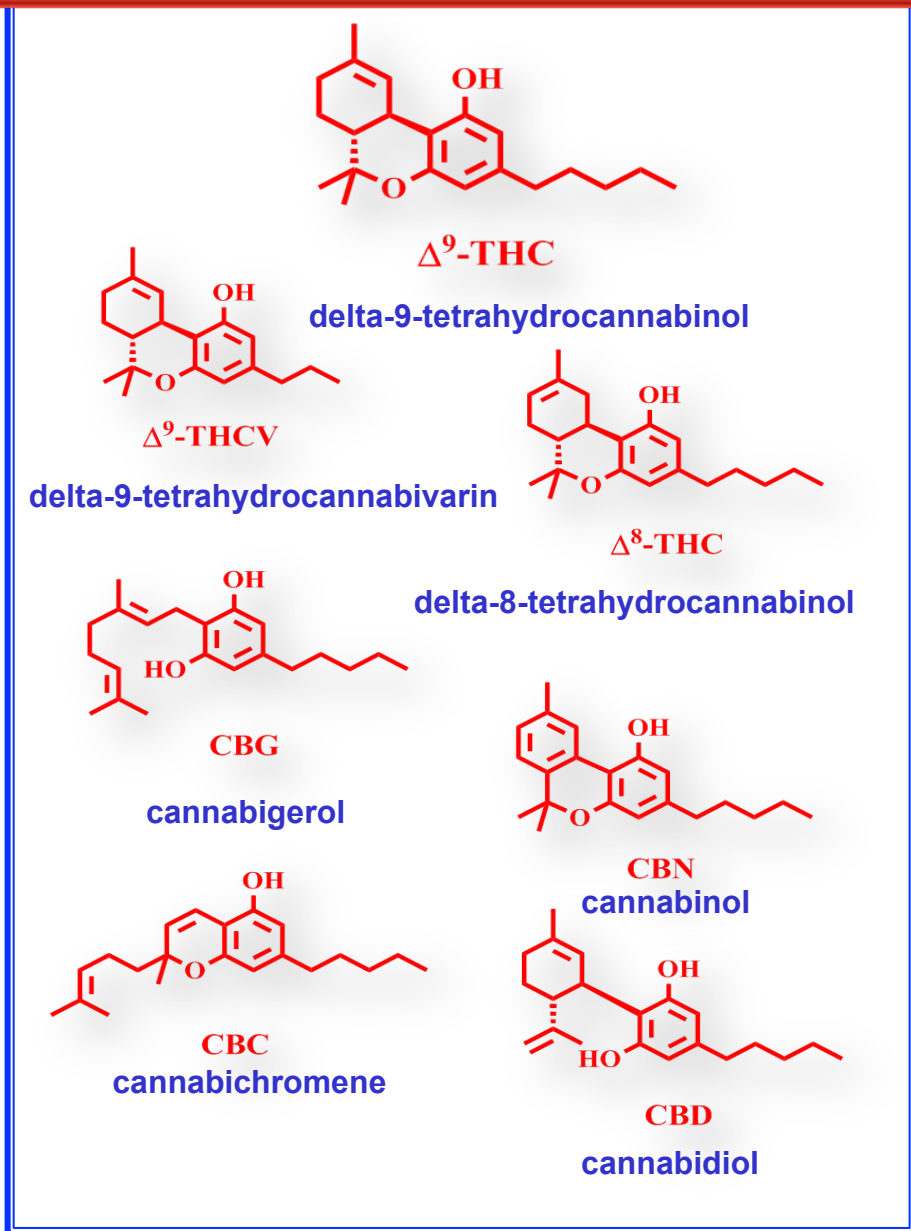
# Natural and Drug Reinforcers Increase Dopamine in NAc



Drugs of abuse increase DA in the Nucleus Accumbens, which is believed to trigger the neuroadaptations that result in addiction

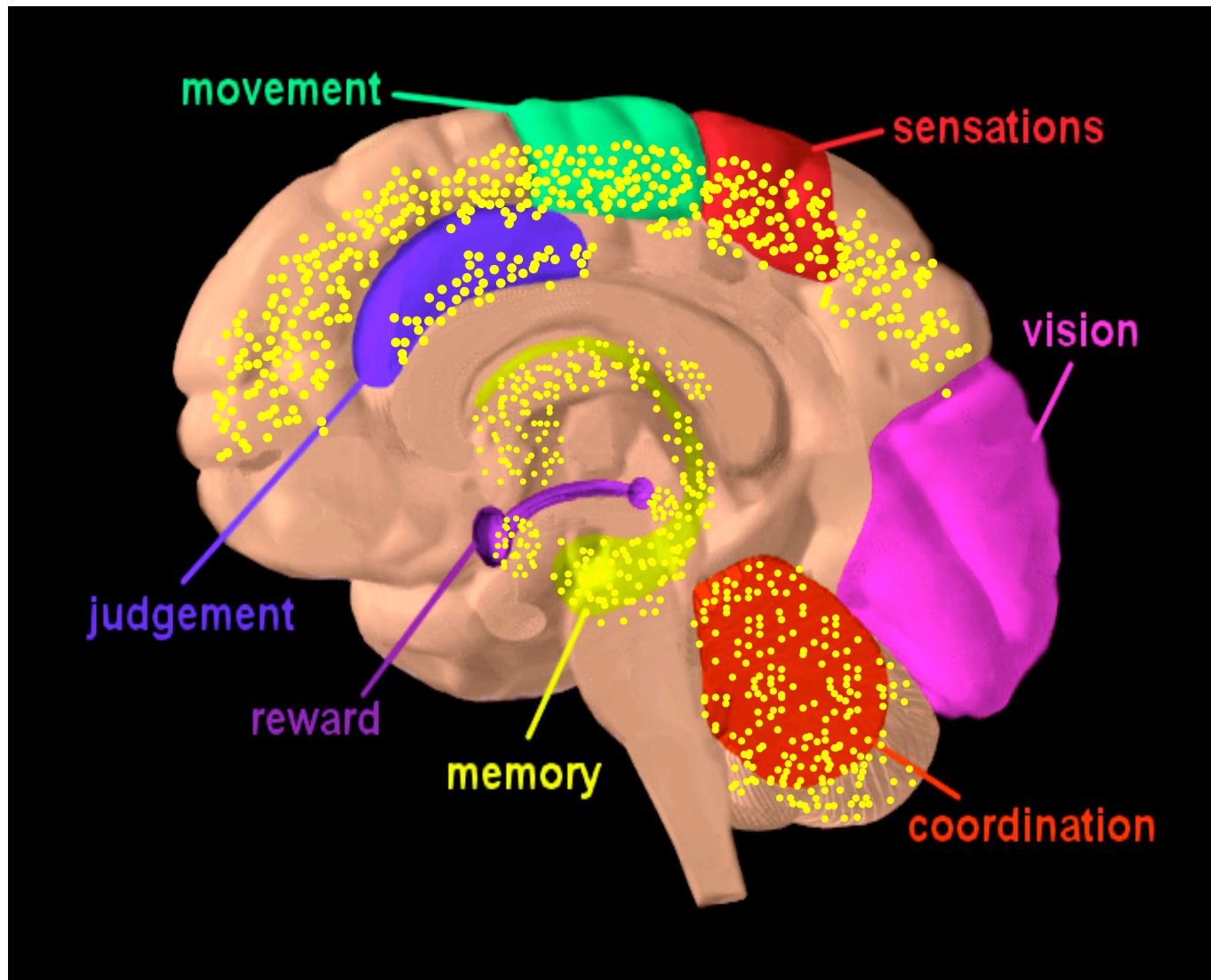


# Constituents of MJ and the Cannabinoid System



# Cannabinoid Receptors Are Located Throughout the Brain and Regulate:

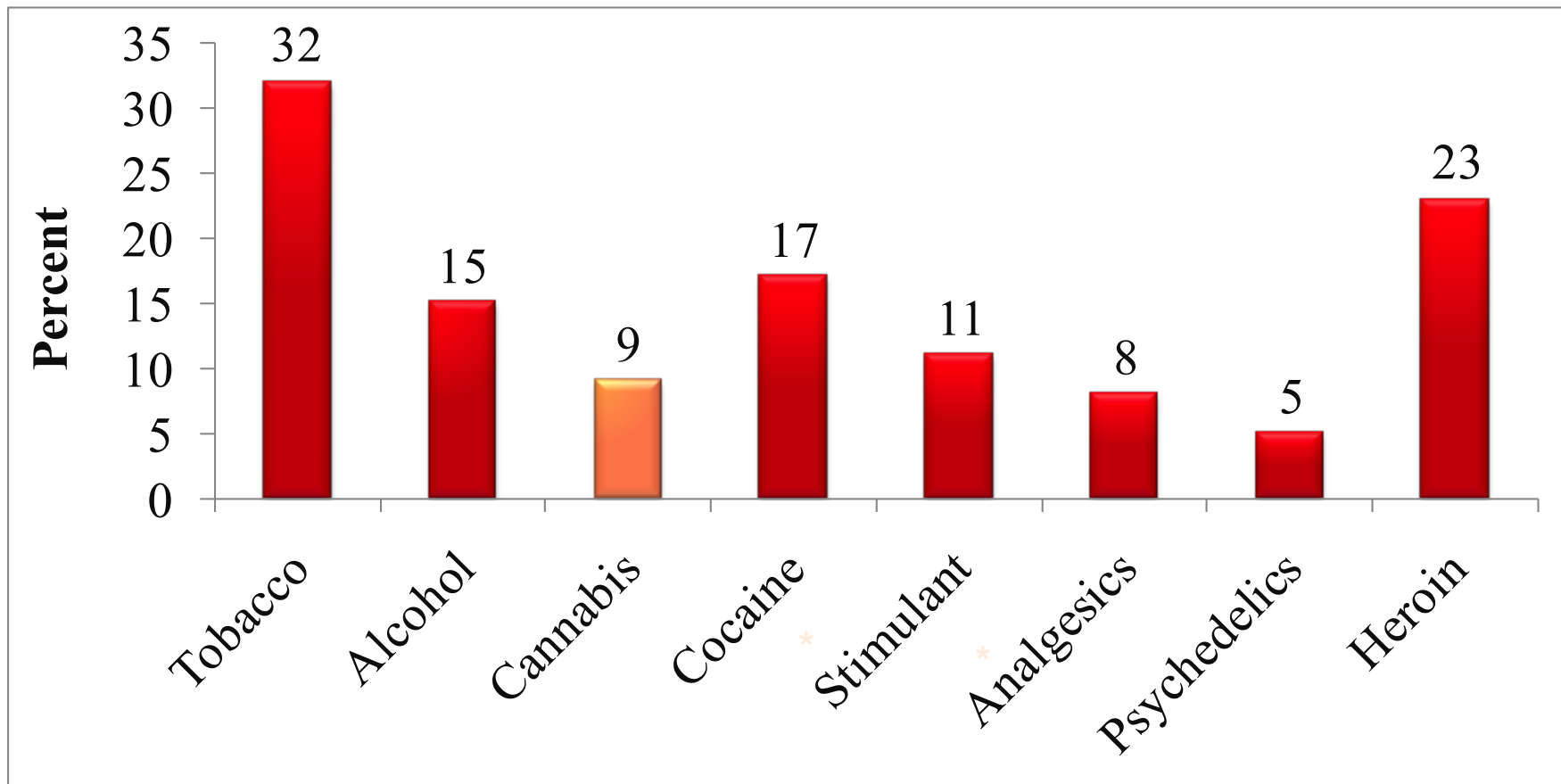
- Brain Development
- Memory & Cognition
- Motivational Systems & Reward
- Appetite
- Immunological Function
- Reproduction
- Movement Coordination
- Pain Regulation & Analgesia



# Long Term Effects of Marijuana

**Addiction:** About 9% of users may become dependent, 1 in 6 who start use in adolescence, 25-50% of daily users

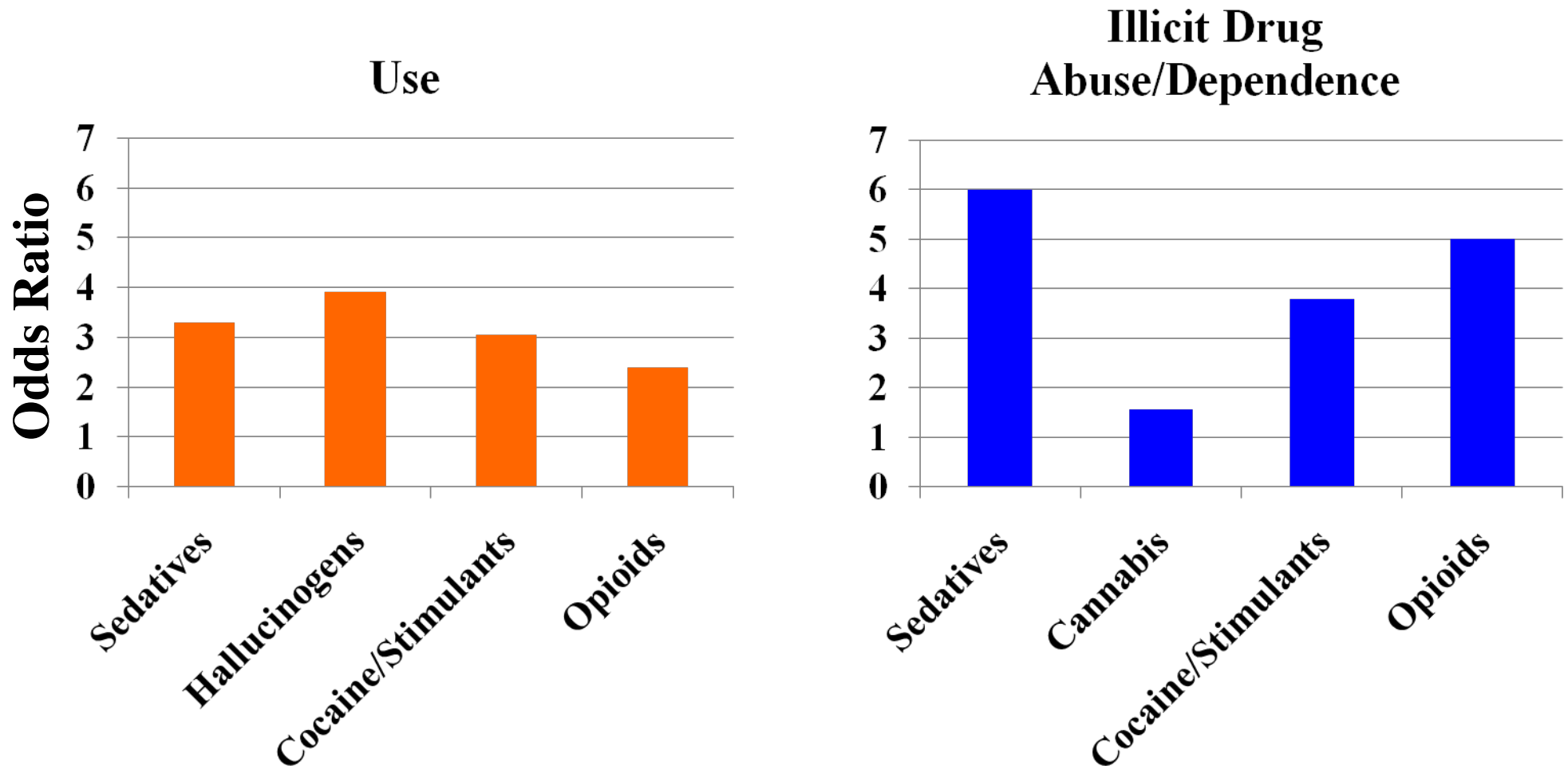
## Estimated Prevalence of Dependence Among Users



*\* Nonmedical Use*

*Source: Anthony JC et al., 1994*

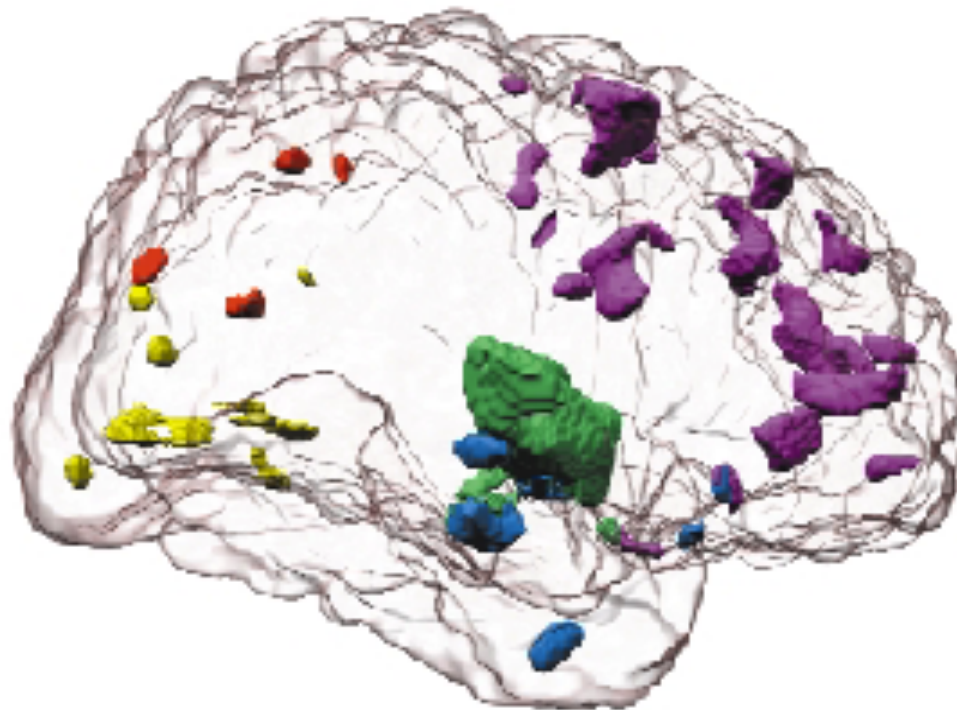
# Drug Use Outcomes in Twin Pairs (n =234) Discordant for Cannabis Use Before Age 17



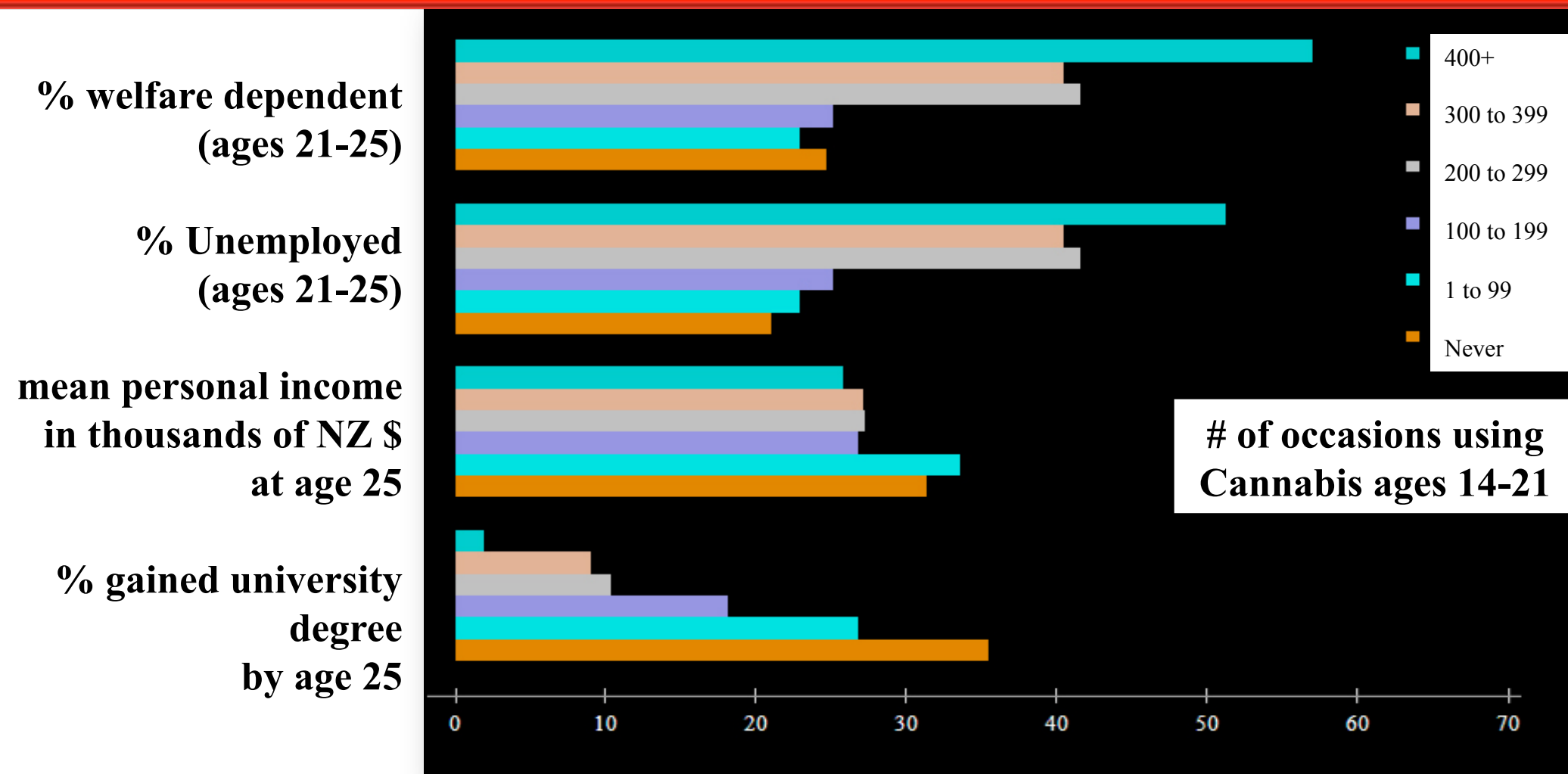
Source: Lynskey, MT et al., JAMA, 289, pp. 427-433, 2003.



*Does marijuana use negatively affect the developing brain and an individual's personal trajectory into adulthood?*



# Cannabis Use and Later Life Outcomes Are Dose Dependent

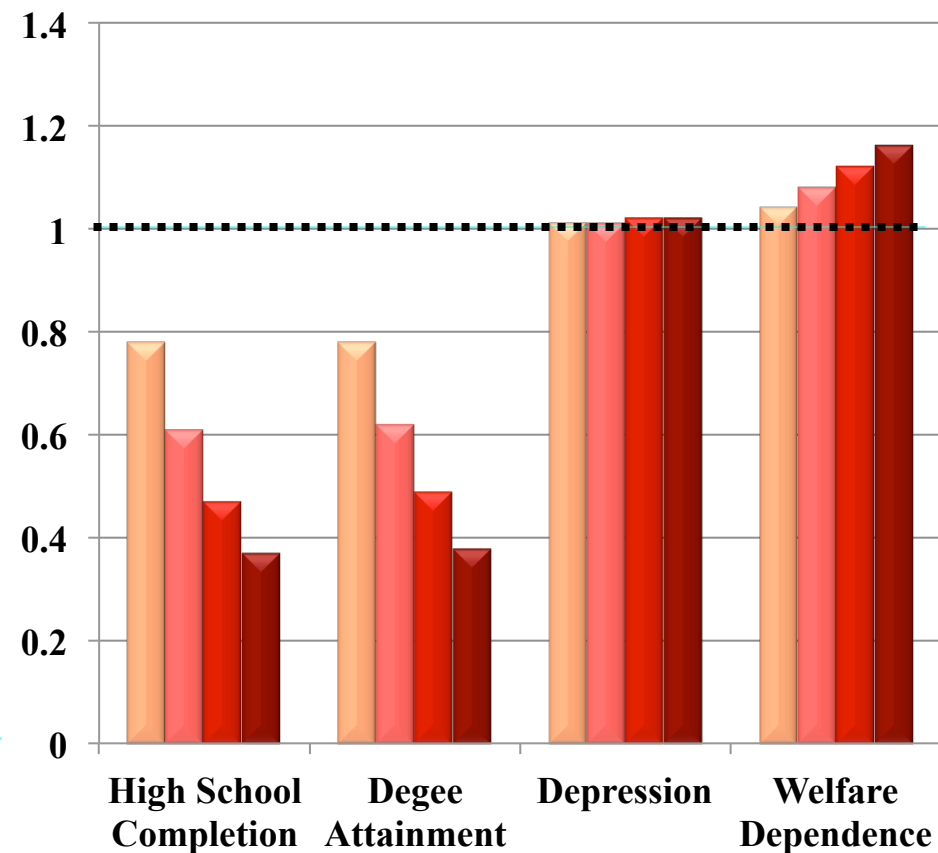
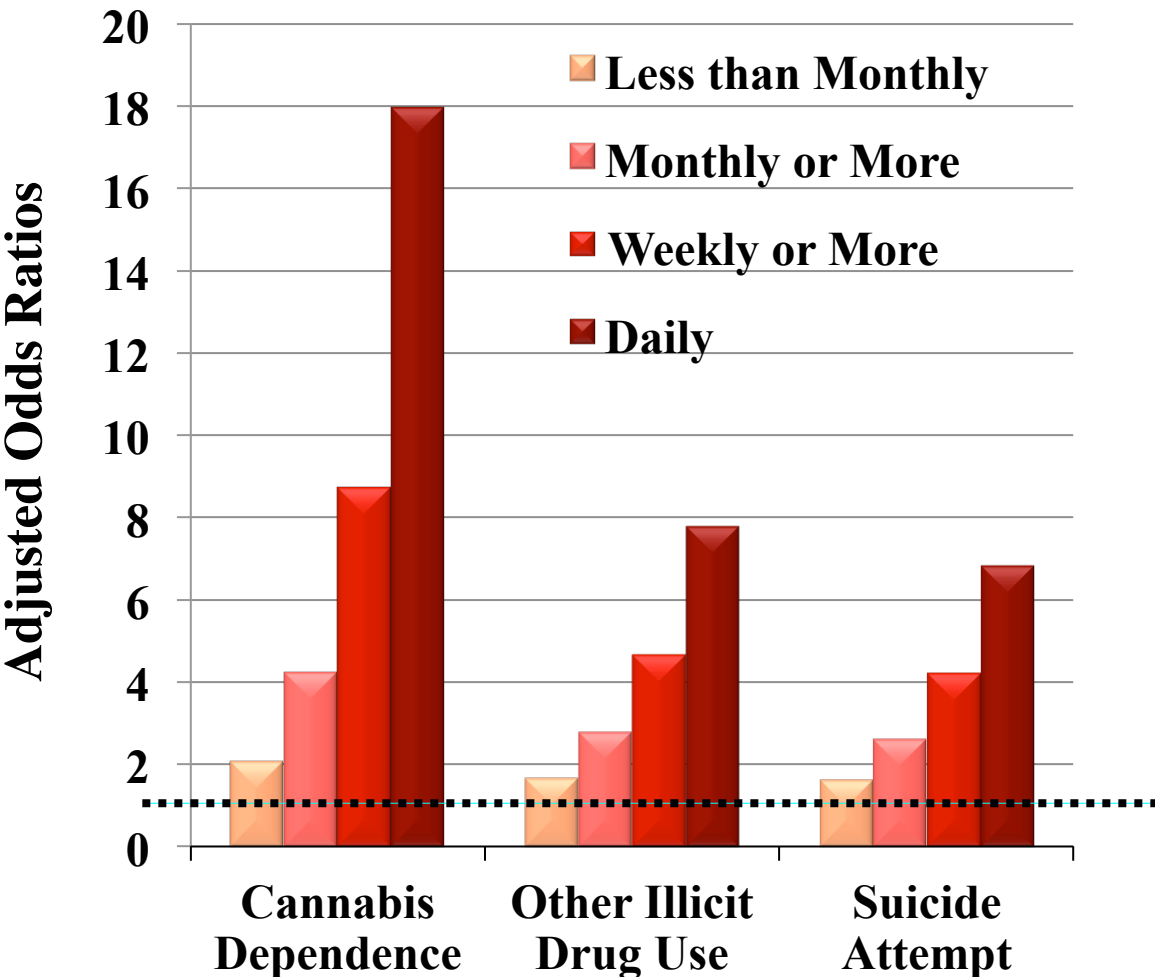


*Source: Fergusson and Boden. Addiction, 103, pp. 969-976, 2008.*



# Frequency Of Cannabis Use Before Age 17 Years and Adverse Outcome (30years age) (n=2500-3700)

Consistent and dose-response association were found between frequency of adolescent cannabis use and adverse outcomes



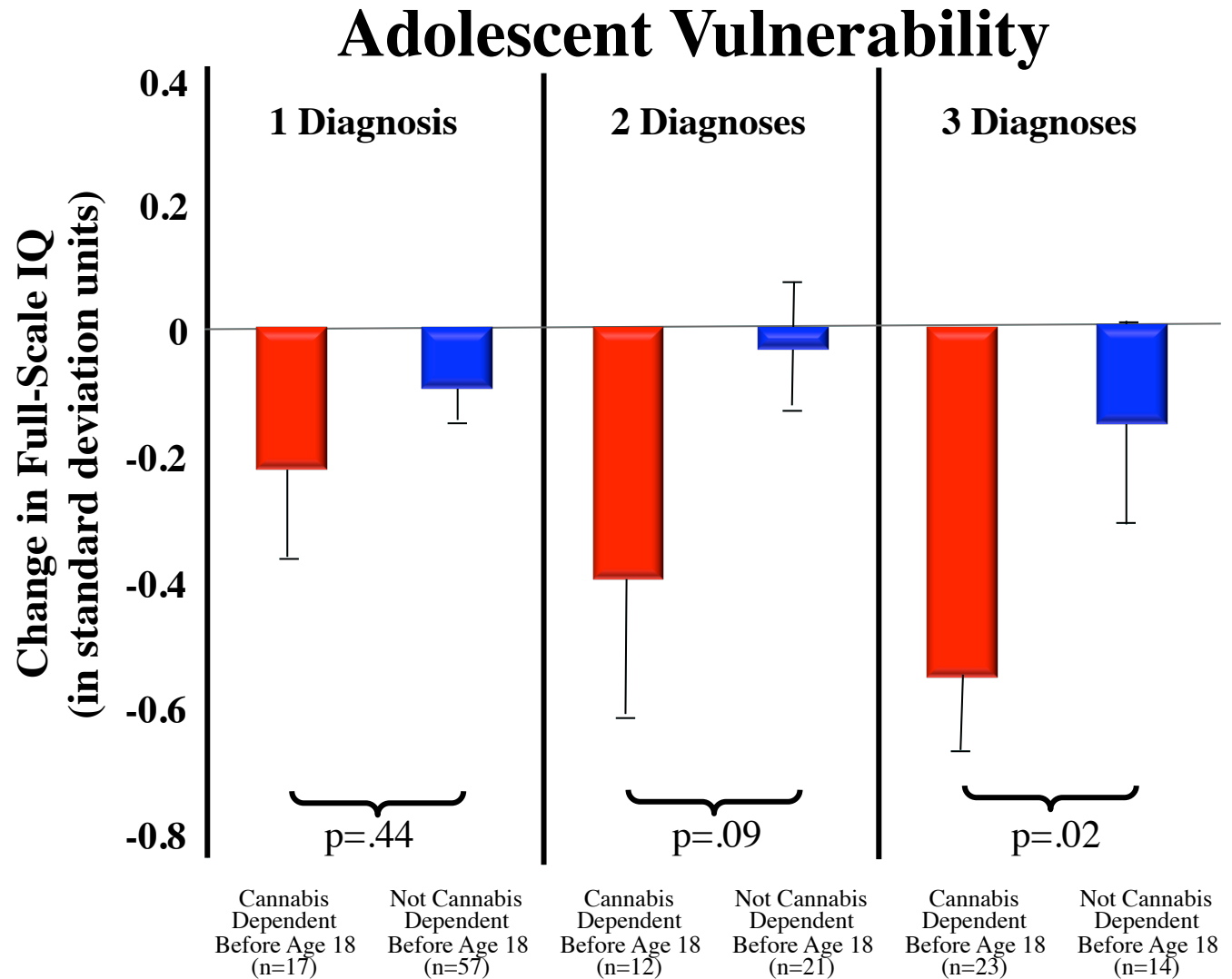
*Silins E et al., The Lancet September 2014.*

# Persistent Cannabis Users Show Neuropsychological Decline from Childhood to Midlife

*Dunedin  
prospective  
study of 1037 Ss  
born 1972/73,*

*Tested for IQ at  
age 13 and 38y.*

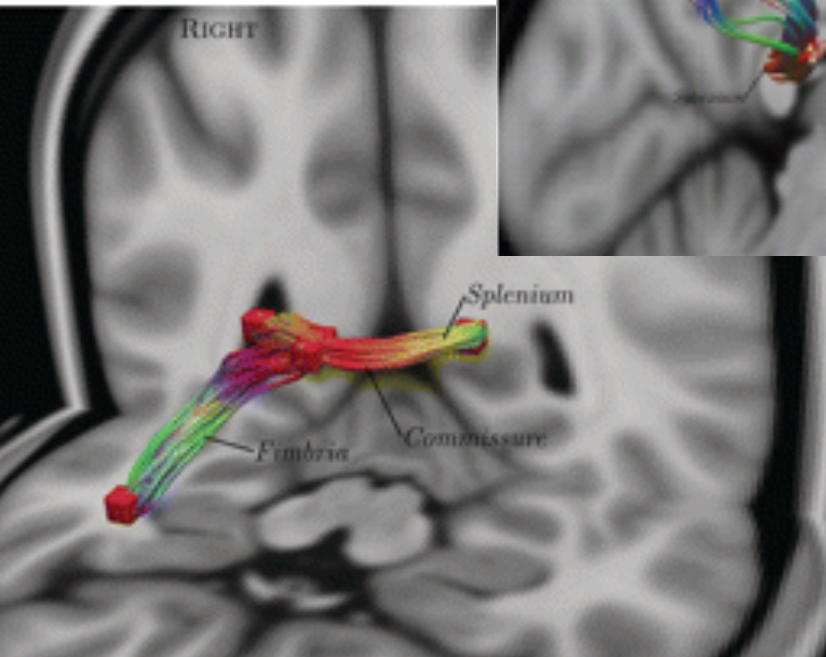
*Tested THC use  
ages 18, 21, 26,  
32 and 38y*



*Source: Meier MH et al., PNAS Early Edition 2012.*

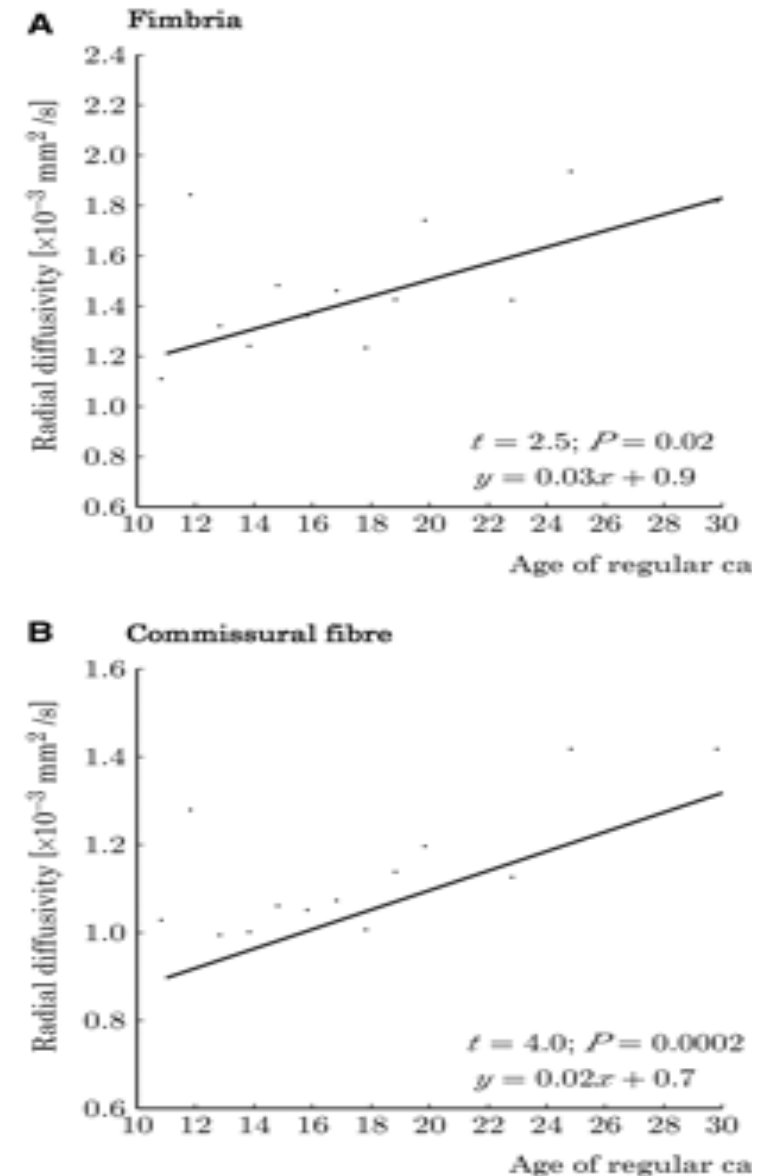
# Early (<18y) Long-Term Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal commissure and Splenium

Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33). *Zalesky et al Brain 2012.*



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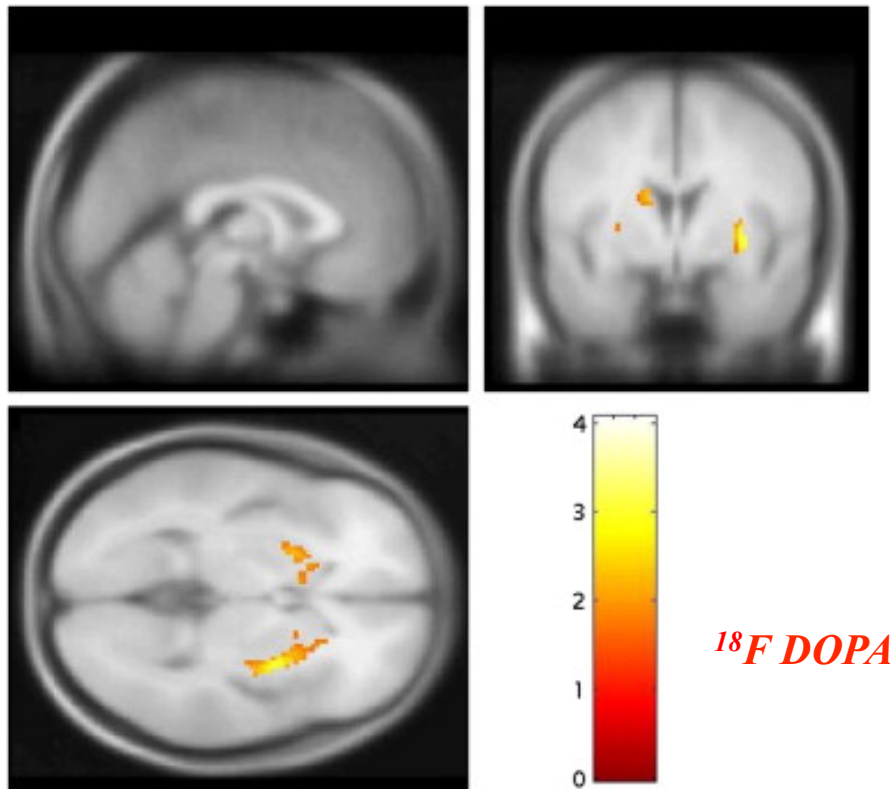
# AMOTIVATION & THC

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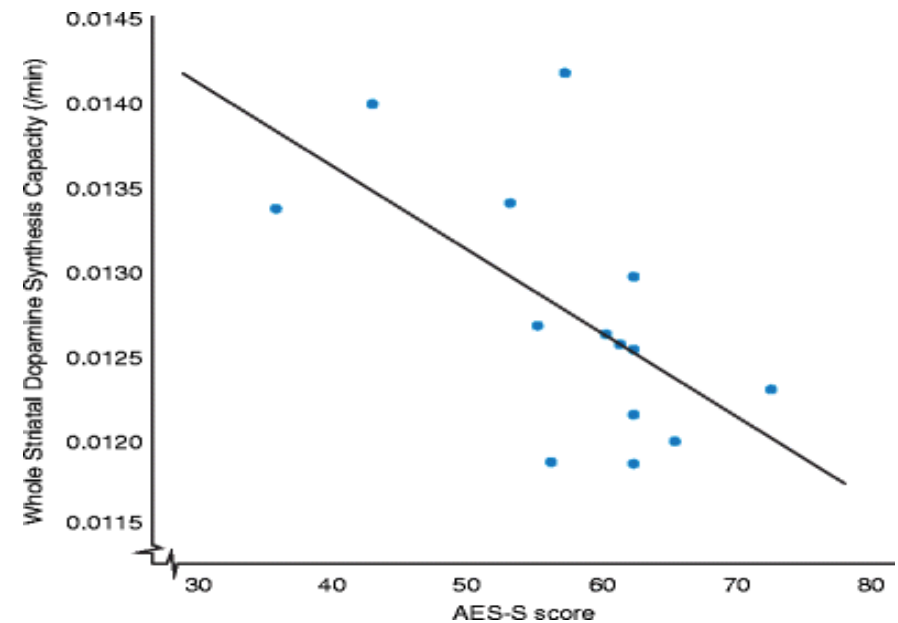


# DA Synthesis Capacity in Cannabis Abusers

*Reduced striatal DA synthesis capacity in cannabis users relative to controls*



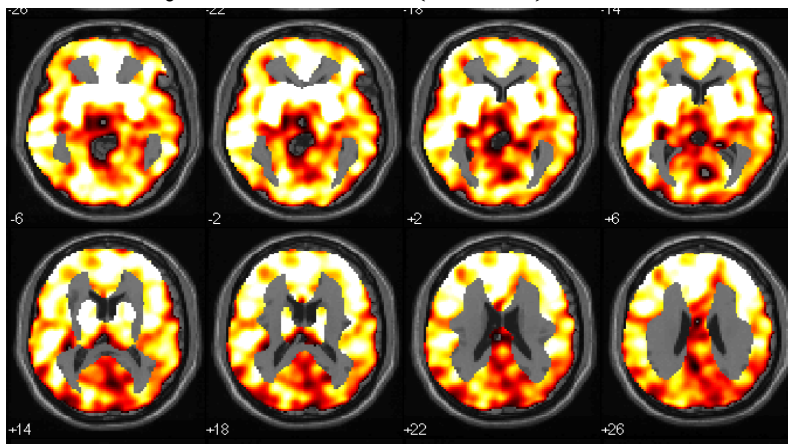
*Striatal DA synthesis and apathy (AES-S score)*



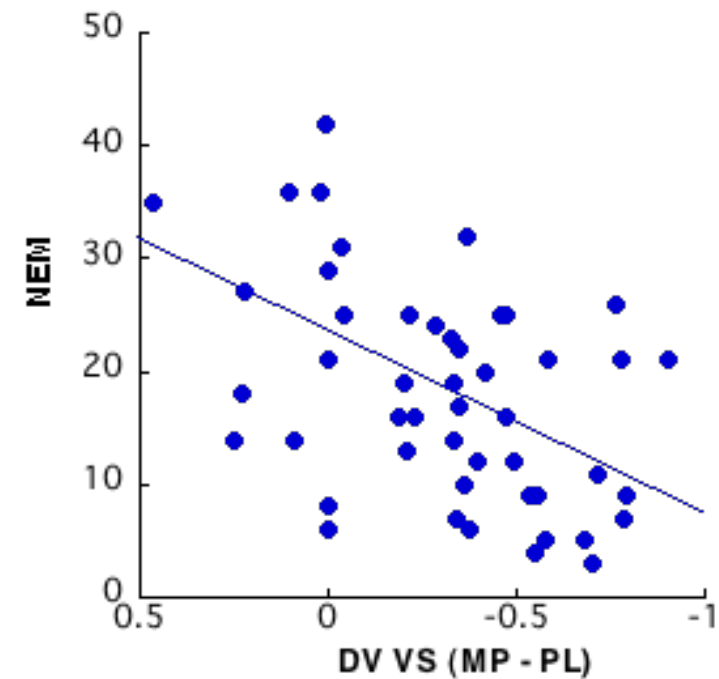
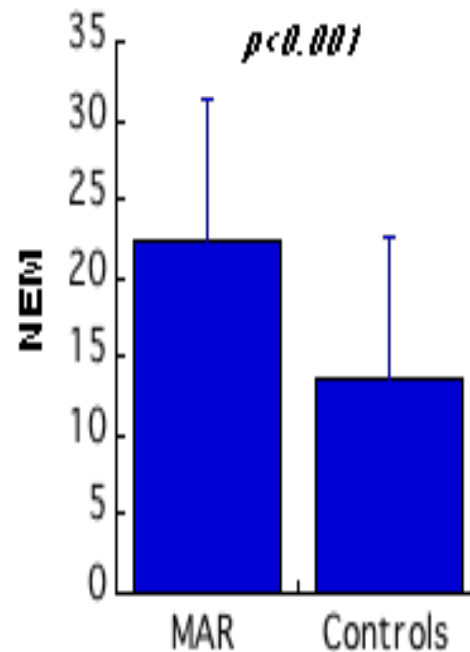
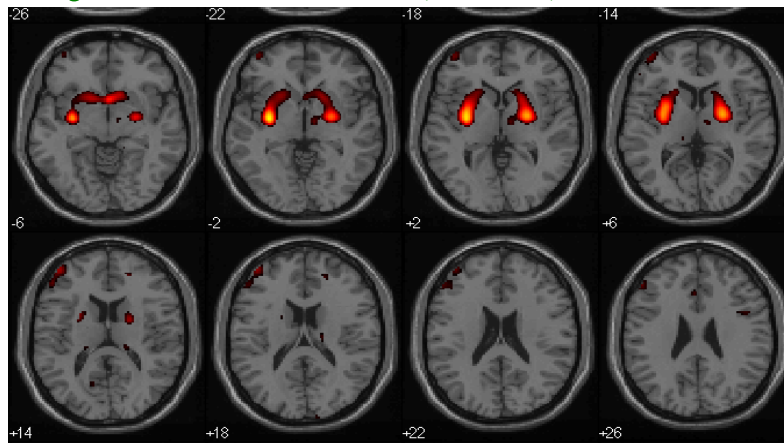
*Bloomfield et al., Psychopharm 2014.*

# MP Induced Changes in [ $^{11}\text{C}$ ]Raclopride (DA Marker) in Marijuana Abusers and Negative Emotionality

Healthy Controls (N=24) PL > MP



Marijuana Abusers (N=24) PL > MP



*Reduced DA reactivity in VS in Marijuana abusers is associated with negative emotionality (NEM)*

*Volkow et al., PNAS 2014*



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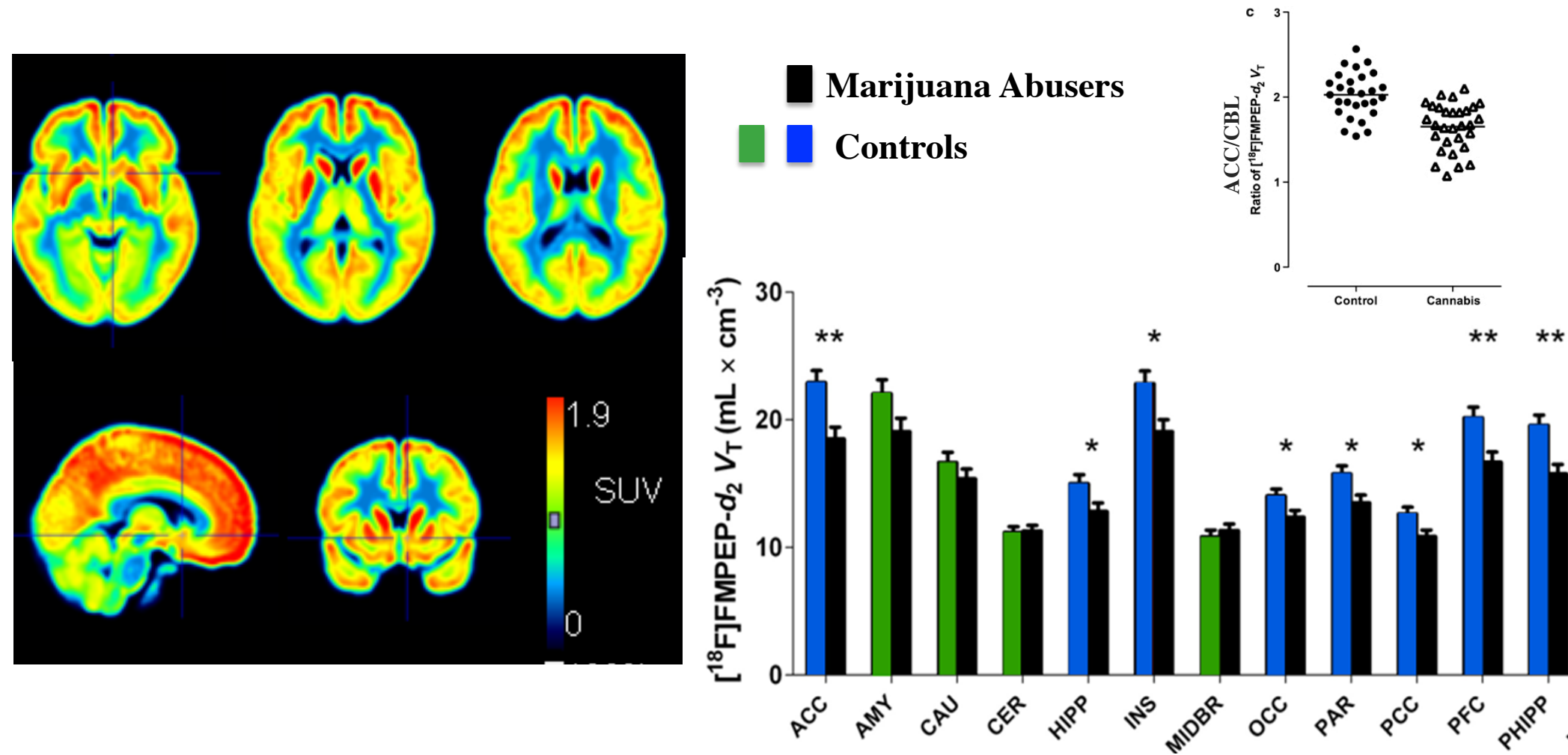
# Effects of THC on Mental Illness

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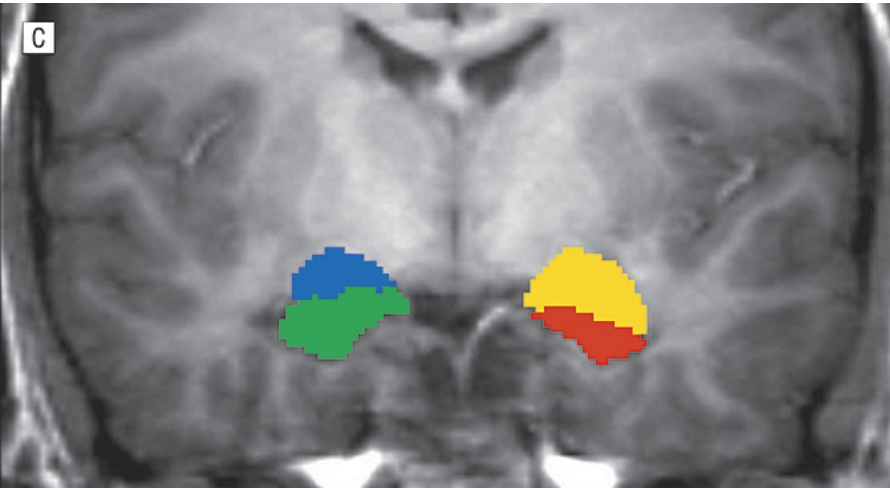
# Cannabinoid CB1 Receptors in Human Brain are Downregulated in Marijuana Abusers



*Van Loere et al., 2007.*

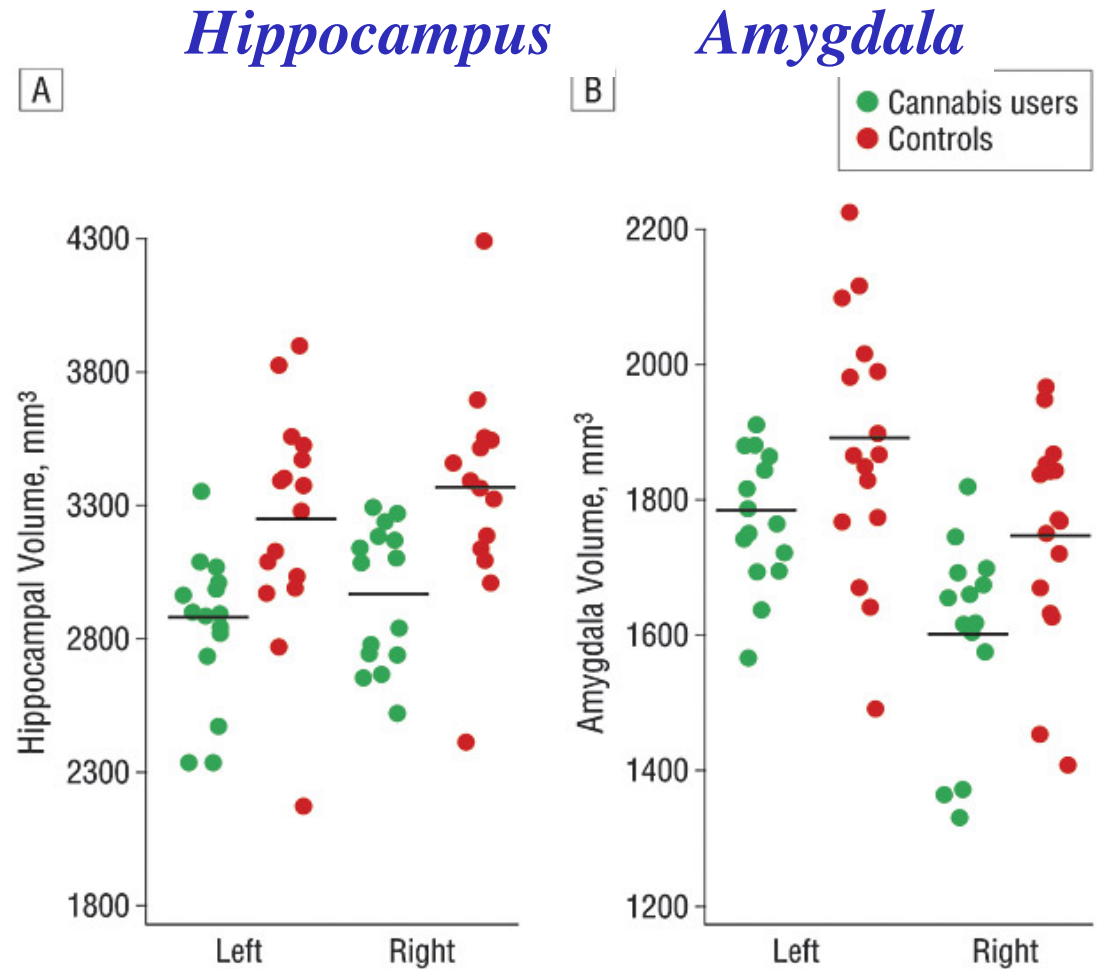
*Hirvonen et al., Mol Psychiatry 2013*

# *Brain abnormalities associated with long-term heavy cannabis use*



L (yellow) and R (blue) amygdala  
L(red) and R(green) hippocampus

*morphology and function of hippocampus has been linked to reduced memory performance in heavy cannabis users*



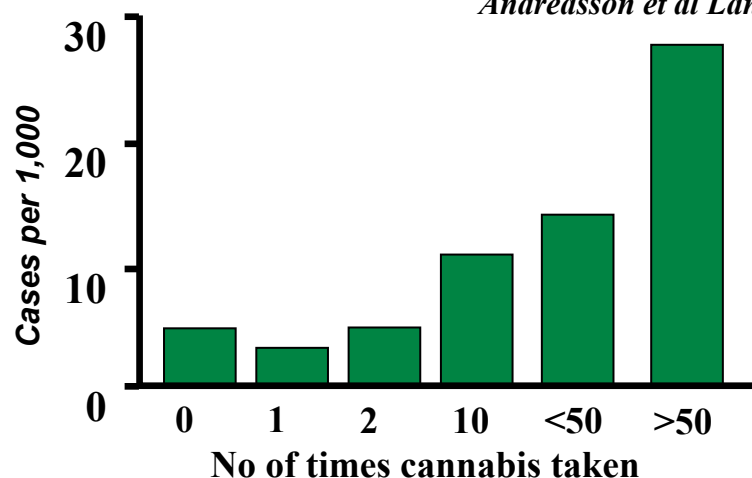
*Hippocampal and amygdalar volumes were smaller in cannabis users than in controls.*

*Yucel et al., Arch Gen Psychiatry. 2008 Jun;65(6):694-701.*

# Cannabis-Associated Psychosis

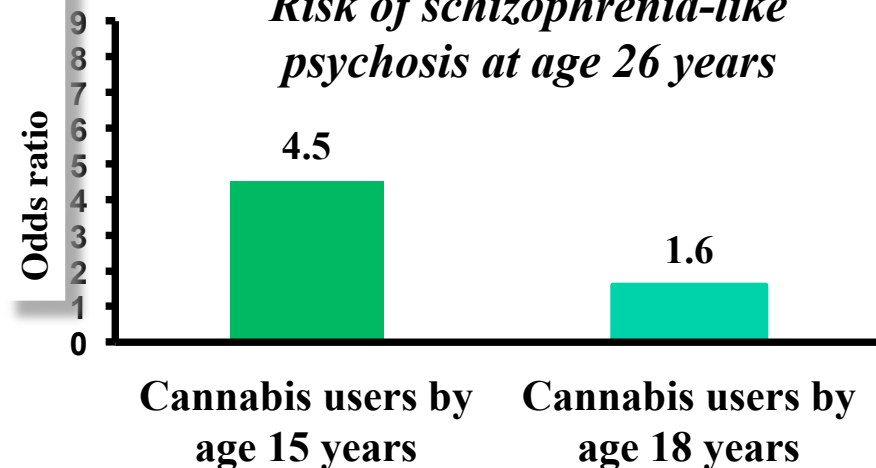
## Study of Swedish Conscripts (n=45570)

*Andréasson et al Lancet, 1987.*



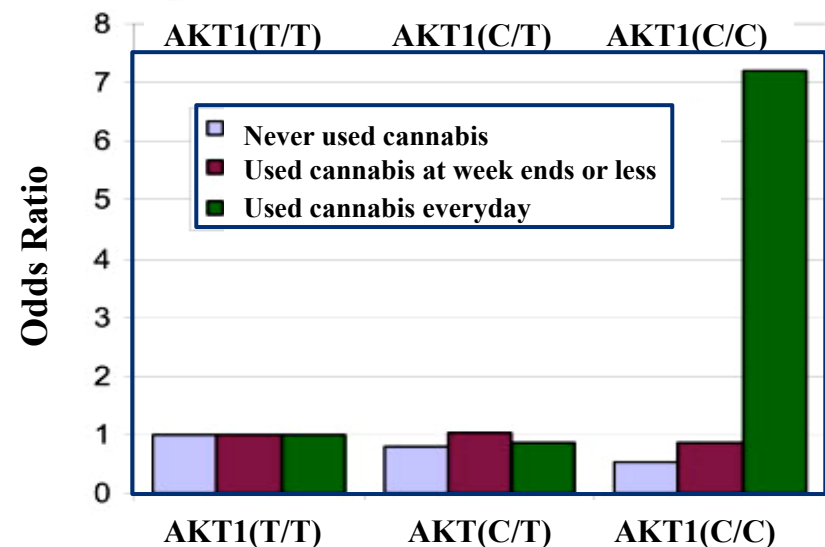
## Prospective Dunedin study (n=1037)

*Risk of schizophrenia-like psychosis at age 26 years*



*Arseneault et al BMJ 2002*

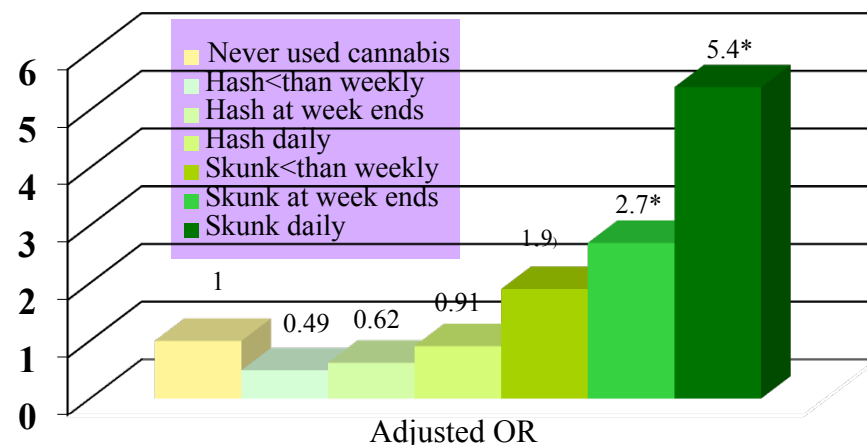
## Regular Cannabis Use Increases Schizophrenia Risk in those with AKT1



GXE model:  $p^*=0.014$

*Di Forti et al., Biological Psychiatry, 2012.*

## Effect of High Potency Cannabis on Risk of Psychosis



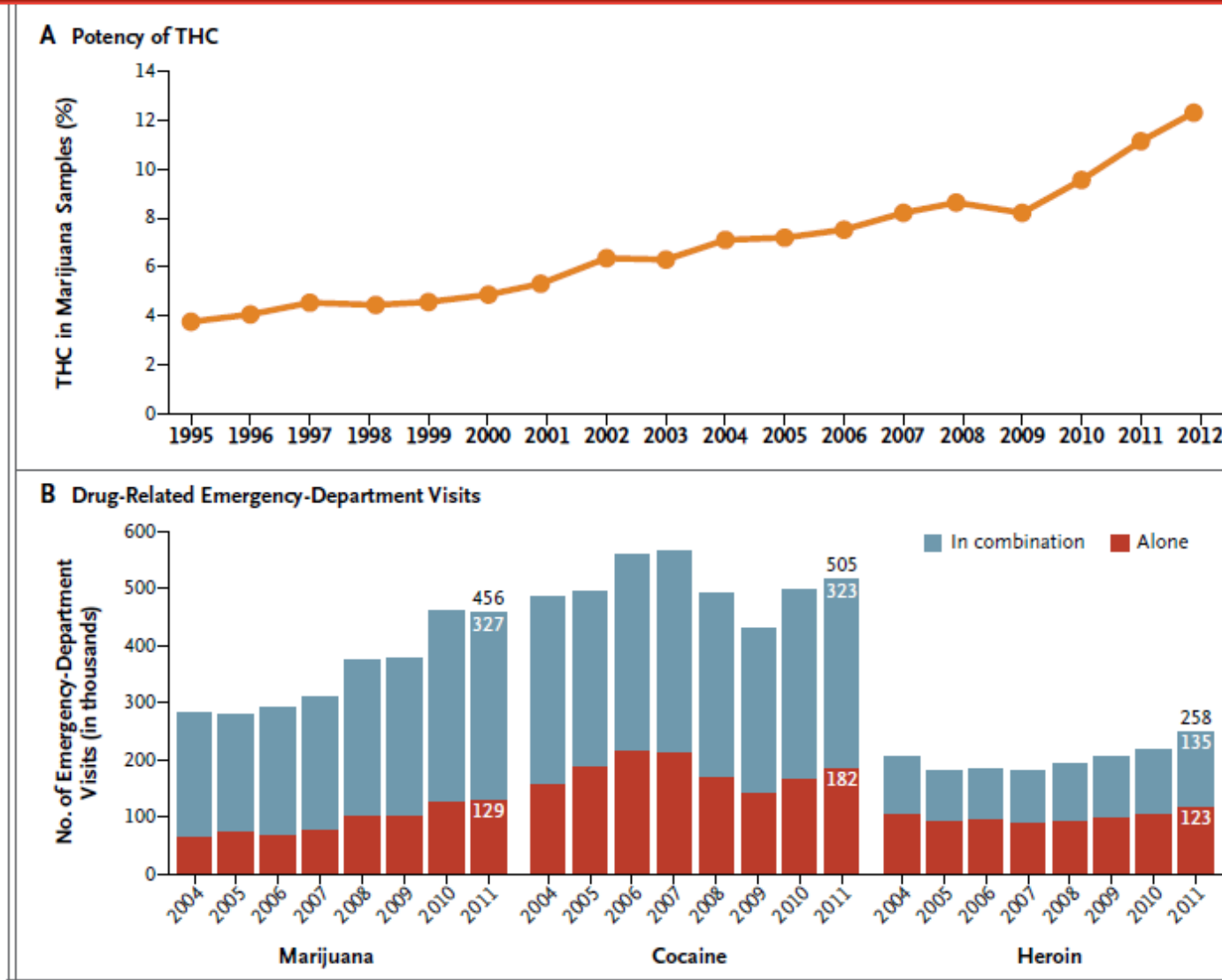
*Di Forti M et al., The Lancet published online February 18, 2015.*



# THC OF TODAY

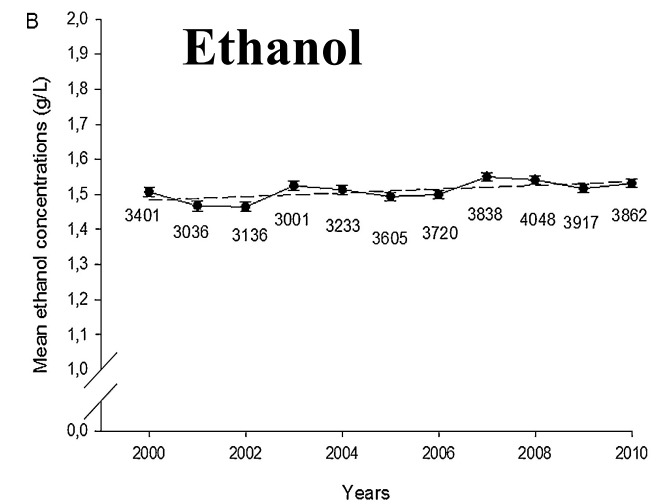
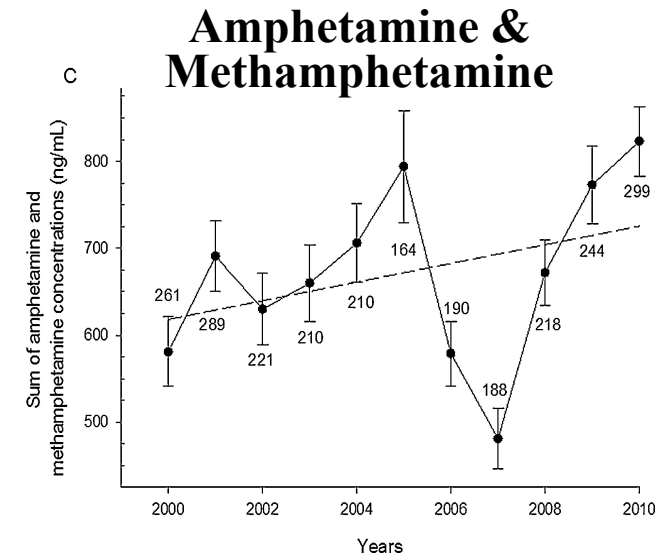
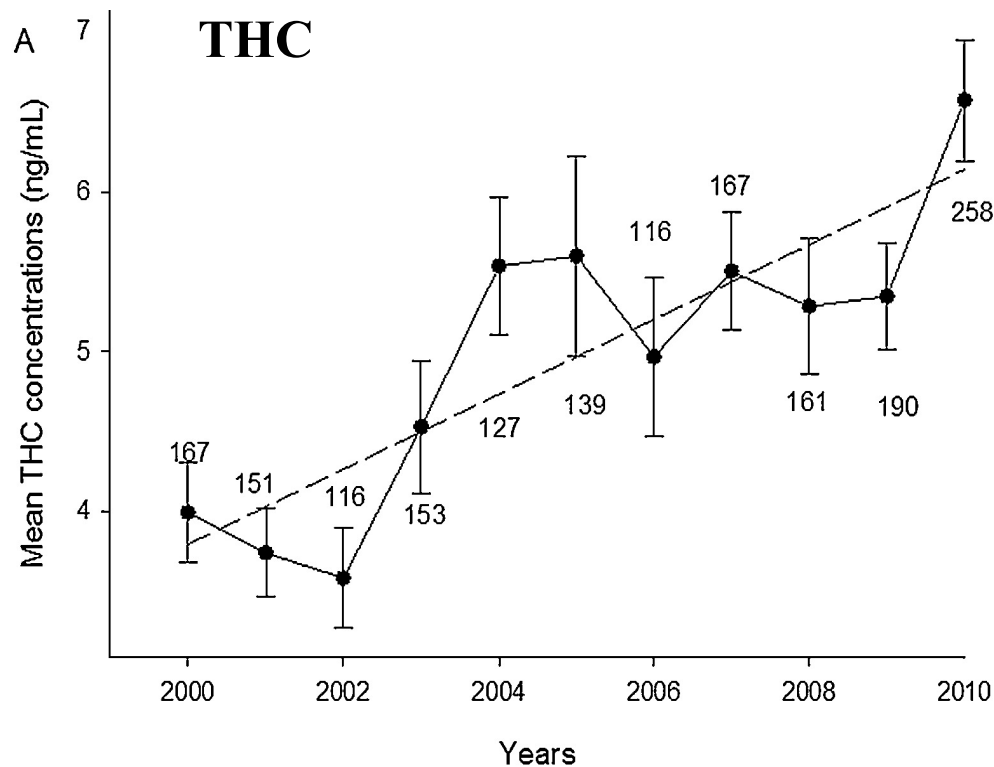


# Increases over Time in the Potency of Tetrahydrocannabinol (THC) in Marijuana and the Number of Emergency Department Visits Involving Marijuana, Cocaine, or Heroin



*Volkow ND et al., NEJM 370(23), June 5, 2014.*

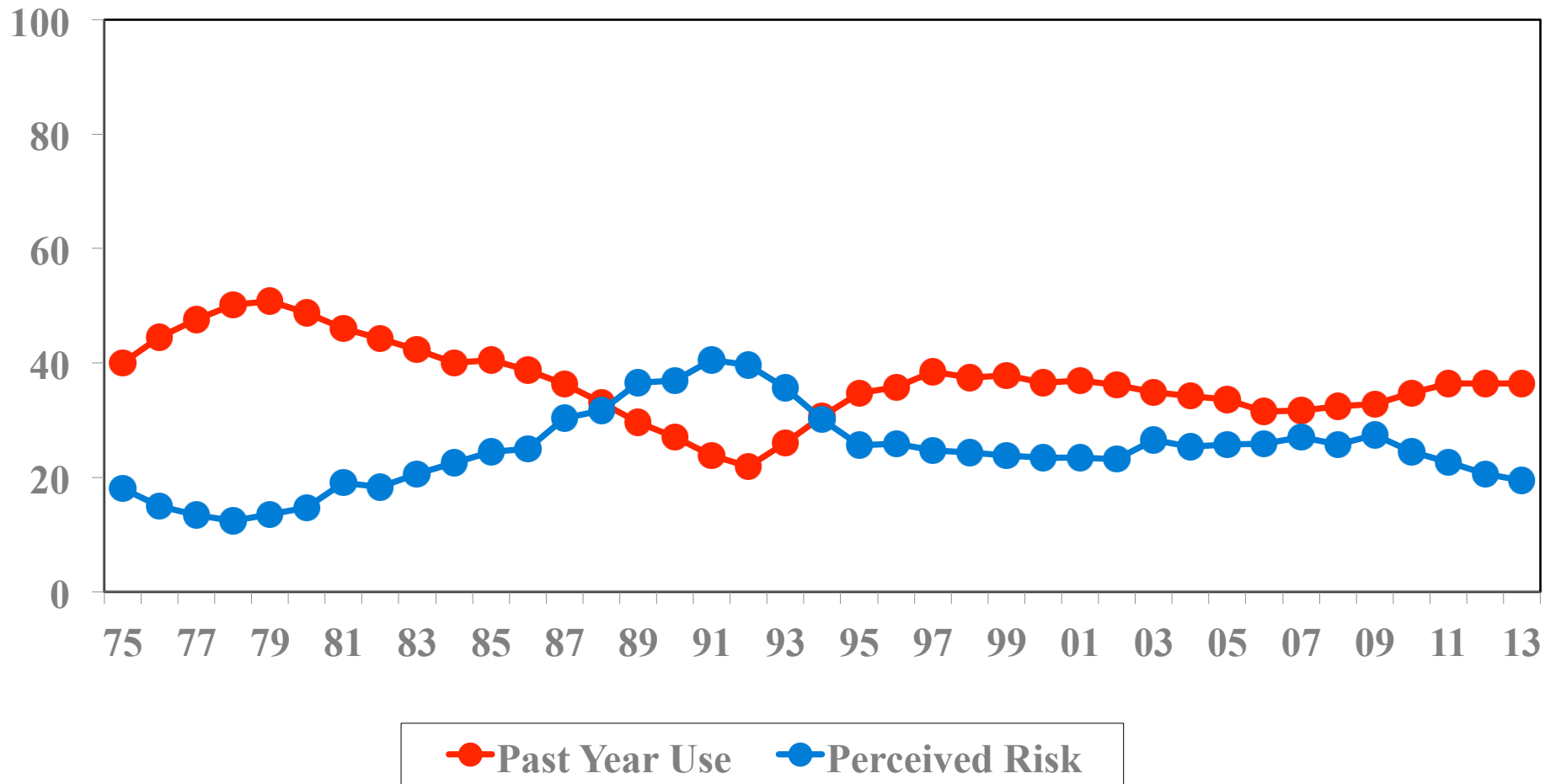
# Mean Concentrations of THC, Ethanol & Amphetamines In Whole Blood Samples From Drivers Apprehended By The Police Suspected Of Driving Under The Influence



*Vindenes V et al., Forensic Sci Internati 2013; 226(1-3): 197-201.*

# SUBSTANCE ABUSE IS **PREVENTABLE**

## 12<sup>th</sup> Graders' Past Year Marijuana Use vs. Perceived Risk of Occasional Marijuana Use



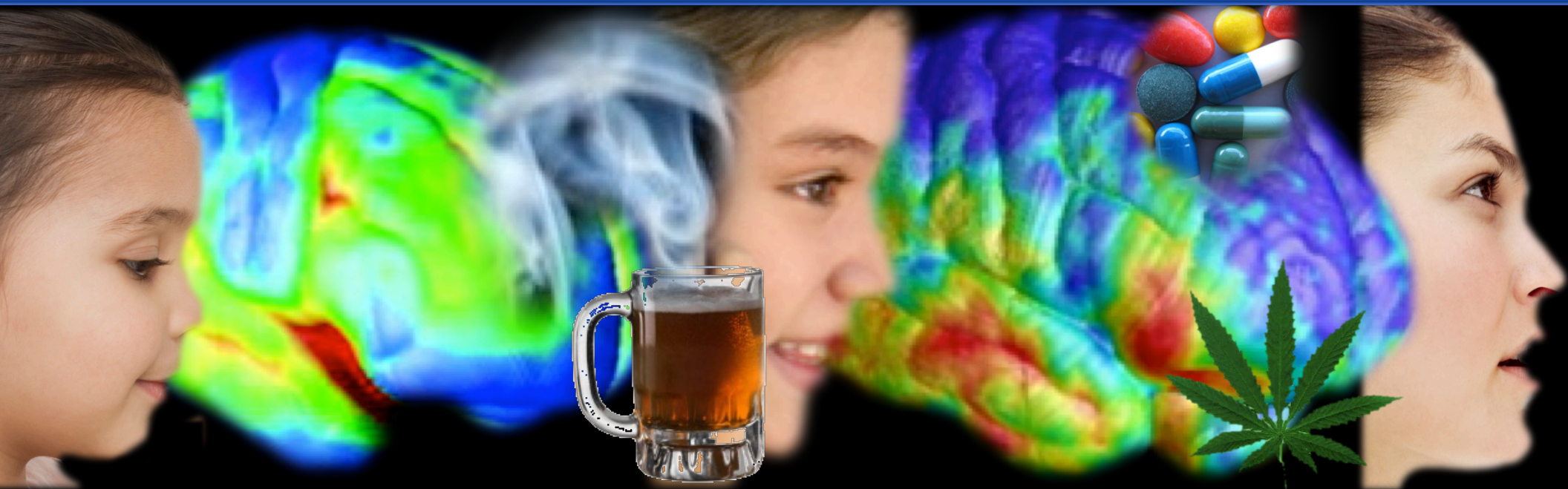
*SOURCE: University of Michigan, 2013 Monitoring the Future Study*



# Adolescent Brain Cognitive Development National Longitudinal Study

NIDA, NIAAA, NCI, NICHD, NIMHD, NIMH, NINDS, OBSSR

*Ten year longitudinal study of 10,000 children from  
age 10 to 20 years to assess effects of drugs on  
individual brain development trajectories*



# Subcortical Structures Differences Between Regular Marijuana Users and Nonusers

